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Feature Article

Serotonergic Dysfunction, Negative Mood States, and Response to Alcohol

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Background: Dysfunction of central serotonergic neurotransmission has been implicated in the pathogenesis and maintenance of alcoholism. Serotonergic dysfunction may be associated with three behavior patterns relevant for alcoholism: impulsive aggression, negative mood states, and a low response to alcohol intake.

Methods: We reviewed the literature on the psychopathological correlates of serotonergic dysfunction and focused on studies that assess the interaction between negative mood states and alcohol response.

Results: Prospective studies in nonhuman primates that underwent early separation stress found an association between a low serotonin turnover rate and the disposition to excessive alcohol intake and impulsive aggression. These findings seem to be relevant for a subgroup of alcoholics with a low serotonin turnover rate and antisocial personality traits. Cross-sectional data in humans also support a relationship between reduced serotonergic neurotransmission and aggressive behavior and indicate that the association of serotonergic dysfunction and aggression may be mediated by negative mood states. This hypothesis is in accordance with a large body of data linking anxiety and depression to serotonergic dysfunction. In human alcoholics, brain imaging has detected a reduction in serotonin transporter availability in association with depression. Serotonin transporter availability seems to be related to reduced GABA-ergic sedation and the acute response to alcohol intake, an important predictor of subsequent development of alcohol dependence.

Conclusions: Several lines of evidence point to a relationship between serotonergic dysfunction, negative mood states, and excessive alcohol intake, which may be mediated in part by reduced alcohol-induced sedation.

Key Words: Serotonin Transporters, SLC6A4 - Level of Response to Alcohol, Impulsivity, Negative Mood States.

PSYCHOPATHOLOGICAL CORRELATES OF SEROTONERGIC DYSFUNCTION

Serotonergic pathways originate in brainstem raphe nuclei and project to numerous subcortical and cortical areas of the brain (Baumgarten and Grozdanovic, 1997). The innervation of widespread areas of the brain is consistent with the multitude of functions modulated by serotonin and the variety of psychiatric disorders in which dysfunction of serotonergic neurotransmission has been observed (Cloninger, 1987b; Grove et al., 1997; Meltzer et al., 1994; Owens and Nemeroff, 1994). Serotonergic dysfunction has been implicated in the pathogenesis and maintenance of excessive alcohol consumption and alcohol dependence (Fils-Aime et al., 1996; Le Marquand et al., 1994a,b). At least three mechanisms, namely, disinhibition, enhancement of anxiety, and altered alcohol response, have been proposed to explain the relationship between serotonin and alcoholism.

Serotonin is an important modulator within the so-called behavior inhibition system (BIS) (Gray, 1982), and it has therefore been suggested that low serotonin turnover leads to behavior disinhibition, early onset of alcoholism, and impulsive aggression (Cloninger, 1987a,b; Kruesi et al., 1990; Linnoila et al., 1983; Virkunnen et al., 1994). This idea is also supported by pharmacobehavioral studies in rodents relating serotonin to irritable aggression and excessive alcohol intake (Crabbe et al., 1996; Saudou et al., 1994). In recent years, there have also been indications that two serotonin genes, 5-HT_{1B} and tryptophan hydroxylase (TPH), may be linked to the impulsive or antisocial dimensions of behavior in alcoholics (Lappalainen et al., 1998; Nielsen et al., 1998). It should be pointed out, however,

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that these population associations and sib-pair linkages were to genetic markers and not functional alleles ("candidate alleles").

Serotonergic dysfunction also seems to be a cause of negative mood states, namely, anxiety and depression (Artigas, 1995; Barr et al., 1994; Mann et al., 1996; Traskman-Bendz et al., 1984; van Praag, 1977). Among alcoholics, the association between serotonergic dysfunction and depression is less well established. Some genetic linkage and brain imaging studies, however, have suggested that a reduced availability of serotonin transporters is associated with anxiety and depressed mood states among alcoholics, patients with major depression, and control subjects (Heinz et al., 1998b; Lesch et al., 1996; Malison et al., 1998; Mazzanti et al., 1998; Rosenthal et al., 1998).

Serotonin also seems to alter the short-term response to acute alcohol (Doudet et al., 1995; Heinz et al., 1998a; Schuckit et al., 1999). Data on this topic are preliminary yet interesting, because a low level of response to acute alcohol intake is more common in the relatively alcohol-naive offspring of alcoholics and is predictive of subsequent alcohol abuse and dependence (Rodriguez et al., 1993; Schuckit and Smith, 1996; Volavka et al., 1996). In this review, we will trace these three lines of evidence and examine whether a coherent view of serotonergic dysfunction in alcoholism may be emerging.

SEROTONERGIC DYSFUNCTION, IMPULSIVE AGGRESSION, AND DISPOSITION TOWARD ALCOHOL DEPENDENCE

The neurobiologies of the predisposition and maintenance of alcohol dependence are divergent. Among alcoholics, the causes and consequences of chronic alcohol intake are often hard to distinguish (Le Marquand et al., 1994b). Therefore, it is important to examine animal models in which factors that may contribute to the development of alcohol abuse and dependence, such as alcohol preference, can be assessed under controlled conditions. In such models, serotonin function in preferring and nonpreferring animals can be assessed before and after chronic ethanol (Higley et al., 1996; Le Marquand et al., 1994a). Mash and others (1996) observed a low serotonin and dopamine turnover rate and an increased availability of dopamine transporters among alcohol-preferring primates compared with nonpreferring primates before the onset of regular alcohol consumption (Mash et al., 1996). After chronic alcohol intake, both serotonin and dopamine turnover increased, and there was a reduction in dopamine transporter density. These observations are in accordance with the monoamine deficit hypothesis of alcohol preference: low dopamine and serotonin turnover rates in alcohol-preferring animals are balanced by alcohol-induced stimulation of dopamine and serotonin release (Gessa et al., 1985; Imperato and Di Chiara, 1986; Le Marquand et al., 1994a). In the shell region of the nucleus accumbens, both dopaminergic and serotonergic stimulation are rewarding (Tomkins and Tampakeras, 1999; Wise, 1988), whereas further serotonin effects on mood and impulsivity may involve other subcortical and cortical serotonergic pathways (Baumgarten and Grozdanovic, 1995; Baxter et al., 1992; Heinz, 1999a). The increment in monoaminergic neurotransmission and the experience of reward, however, may come at the price of secondary neuroadaptive changes, such as reductions in monoaminergic transporters or postsynaptic receptors (Balldin et al., 1992; Mash et al., 1996; Rommelspacher et al., 1992).

In a brain-imaging study with SPECT and the radioligand β-CIT, the availability of serotonin transporters was evaluated in relationship to transporter genotype and cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA) concentrations. The study was performed in adult rhesus macaque monkeys predisposed to excessive alcohol intake by early social separation stress (Heinz et al., 1998a). CSF 5-HIAA was reduced in animals that had been separated from their mothers and peer-raised compared with mother-reared monkeys (Clarke et al., 1996; Higley et al., 1996). Concentrations of 5-HIAA in the CSF decreased further when the primates were completely isolated from their peers. These reductions in CSF 5-HIAA were trait-like and persisted during adulthood (Higley et al., 1996; Heinz et al., 1998a). During early social separation, rhesus macaques displayed increased anxiety-like behaviors (Higley et al., 1991), and during adulthood, the male animals were especially likely to be aggressive (Higley et al., 1996). The low CSF 5-HIAA concentrations in these monkeys were associated with an increased availability of serotonin transporters in the raphe area, reduced time spent in social contacts, and an increased frequency of self-initiated aggressive acts (Heinz et al., 1998a). The primates thus showed some of the behaviors within the impulsive aggressive pattern found in so-called type 2 alcoholics, who also display low CSF 5-HIAA concentrations (Cloninger, 1987a; Fils-Aime et al., 1996).

The increased availability of raphe serotonin transporters in primates with low CSF 5-HIAA concentrations may be due to a real increase in serotonin transporter density. Such biological parallels may be related to the increase in striatal dopamine transporter density seen in monkeys predisposed to excessive alcohol intake (Mash et al., 1996). In a combined microdialysis and β-CIT SPECT study, an increase in monoamine uptake sites was correlated with decreased extracellular neurotransmitter concentrations (Heinz et al., 1999), and conversely, loss or blockade of dopamine or serotonin transporters induces an increase in extracellular neurotransmitter concentrations (Giros et al., 1996; Kreiss and Lucki, 1995), confirming the hypothesis that the availability of monoamine uptake sites regulates extracellular monoamine concentrations. Alternatively, a decreased serotonin concentration in the synapse may be correlated with increased β-CIT binding to serotonin uptake sites

because of decreased competition with endogenous serotonin for binding at serotonin transporter (Jones et al., 1998). In any event, an increased availability of serotonin transporters as assessed with β-CIT SPECT indicates decreased concentrations of synaptic serotonin and 5-HIAA in the CSF (Heinz et al., 1998a).

Genetic and Environmental Effects on Serotonergic Neurotransmission

The nonhuman primate studies indicate that a low serotonin turnover rate may be an intermediate trait that predisposes subjects to aggressive behavior and excessive alcohol intake and may thus be present before chronic alcohol consumption has occurred (Heinz et al., 1998a; Higley et al., 1996; Mash et al., 1996). In nonhuman primate studies, both genetic and environmental factors contribute to the serotonin turnover rate as assessed by the serotonin metabolite 5-HIAA in the CSF (Clarke et al., 1996; Higley et al., 1991; 1993). Among adult primates, heritability of serotonin turnover was 42% (Kaplan et al., 2000). Among humans, heritability accounts for approximately 35% of the variance in CSF 5-HIAA concentrations, and environmental factors play a very important role in the regulation of the serotonin turnover rate (Beck et al., 1984; Oxenstierna et al., 1986). Environmental factors are of special interest if they have long-lasting effects on serotonergic neurotransmission, as has been observed after early social separation stress (Clarke et al., 1996; Higley et al., 1991; 1996). Unstable preadoptive placement was associated with excessive alcohol consumption during adulthood (Cloninger, 1981; Bohman et al., 1982; Bohman, 1996). Environmental effects on serotonin turnover rate, alcohol intake, and impulsive aggression are interesting in the light of several twin and adoption studies that found no indication of a disposition toward violent behavior independent of alcoholism (Bohman et al., 1982; Brennan and Mednick, 1993; Carey, 1996; Johnson et al., 1996). Dysfunction of serotonergic neurotransmission after early social isolation stress (Clarke et al., 1996; Higley et al., 1991; Jones et al., 1992) may be one of the environmental factors predisposing toward both impulsive alcohol intake and violent behavior.

Serotonergic dysfunction in association with impulsivity and aggressiveness may characterize a subtype of alcoholism. In various forms and in its latest and most developed fashion by Cloninger (1987a), it has been suggested that there is a "type 2" alcoholism that is characterized by early disease onset, impulsivity, and antisocial personality traits. Such alcoholics have repeatedly been found to have low serotonin turnover (Fils-Aime et al., 1996; Virkunnen et al., 1994). Some research groups, however, objected that type 2 alcoholism may not describe a specific subtype of alcoholism but simply the co-occurrence of antisocial personality disorder (Irwin et al., 1990; Schuckit et al., 1995) and that serotonergic dysfunction characterizes comorbid antisocial personality disorder rather than alcoholism per se (Coccarro et al., 1989; Kruesi et al., 1990). An early deficit in serotonin turnover rate may predispose some individuals toward impulsive behavior and an early onset of alcoholism; however, this mechanism may be relevant only for a subgroup of alcoholics. These considerations raise the questions of whether a serotonergic dysfunction may also play a role in the maintenance of alcohol dependence and whether other psychopathological correlates besides impulsive aggression can be observed that may interact with the risk of relapse of alcoholics.

PSYCHOPATHOLOGICAL CORRELATES OF CENTRAL SEROTONERGIC DYSFUNCTION: IMPULSIVE AGGRESSION OR NEGATIVE MOOD STATES?

Some authors have also questioned whether there is a specific association between serotonergic dysfunction and impulsive aggression and argued that a dysfunction of serotonergic neurotransmission is more credibly related to anxiety, depressed mood (Artigas, 1995; Knutson et al., 1998; Owens and Nemeroff, 1994; Young et al., 1994), and obsessive-compulsive behavior (Barr et al., 1994). The connections of serotonin to distinct behavioral syndromes may derive from common ground. It has been suggested that socialization is successful only if deviant behavior is punished and if this punishment is experienced as unpleasant (Eysenck, 1967). For this to be the case, the experience of punishment needs to be neurobiologically encoded (Patterson and Newman, 1993). Gray (1982) suggested a punishment-reactive system that resides in the periaqueductal gray, the septum, and the hippocampus. Gray (1982) called this the "behavior inhibition system" (BIS) and further suggested that it is regulated by serotonergic and noradrenergic inputs. Acute stimulation of this system was supposed to inhibit ongoing behavior and would subjectively be experienced as anxiety. Chronic activation of the BIS was supposed to induce depression (Gray, 1982). Reduced function of this system, on the other hand, was supposed to induce disinhibited behavior and would clinically result in impulsivity (Patterson and Newman, 1993).

On the basis of findings that so-called psychopathic individuals displayed reduced anxiety when expecting painful electric shocks, it has been suggested that these individuals show a reduced emotional response to punishment. Their reduced inhibition by the experience of social sanctions may allow the development of a pattern of craving for immediate gratification of desires (Wilson and Herrnstein, 1986). Cloninger (1987b) suggested that it is a reduction in serotonergic neurotransmission that specifically induces a dysfunction of the BIS and leads to the manifestation of impulsive and aggressive behavior. A reduction in central serotonin turnover has been observed in heterogeneous groups of individuals with reductions of behavior inhibition, including children with aggressive behavior, violent suicides, alcoholics, violent criminals, and firesetters. It has

been suggested that "impulsive aggression" is the behavioral characteristic common to all of these individuals (Coccarro et al., 1989; Kruesi et al., 1990; Virkunnen et al., 1994).

The ideas outlined above have been criticized, for various reasons. A first line of evidence questioned the concept of a reduced response to punishment among so-called psychopathic individuals. Newman et al. (1990) found that "psychopaths" do not react less to punishment (Newman et al., 1990); neither were they unable to learn from punishment or withdrawal of reward (Newman and Kosson, 1986). Psychopaths were unable to inhibit behavior and unable to acquire passive avoidance only when they had previously been rewarded for a behavior pattern and were only later punished for it. Patterson and Newman (1993) called this behavioral deficit "attentional rigidity," because subjects were unable to focus attention on a new reinforcement schedule and instead persisted in a previously rewarded behavioral strategy.

It has also been questioned how a dysfunction of serotonergic neurotransmission can induce impulsive behavior. Perhaps the most straightforward hypothesis is that the experience of punishment is associated with a serotonergic activation of the septohippocampal BIS, which is subjectively unpleasant and induces subsequent passive avoidance. Within this model, Cloninger (1987b) suggested that the personality trait of "harm avoidance" depends on sufficient activation of serotonergic neurotransmission, resulting in the further avoidance of punishment. A series of findings, however, indicated that an increase in serotonergic neurotransmission may not be associated with unpleasant emotions. The antidepressive efficacy of selective serotonin reuptake inhibitors (SSRIs) has been attributed to an increase in synaptic serotonin concentrations, an observation that is difficult to reconcile with the notion of serotonergic neurotransmission stimulating a punishment system (Artigas, 1995; Kreiss and Lucki, 1995; Limberger et al., 1990; Muck-Seler et al., 1996). The hypothesis that a serotonin deficit is associated with negative emotions, such as anxiety or depression, is supported by studies in which serotonin depletion induced negative mood states among patients with obsessive-compulsive disorder and in a subgroup of patients with major depression who previously responded to serotonin reuptake inhibition (Barr et al., 1994; Delgado et al., 1990). In accordance with this observation, an increase in a primarily low serotonin turnover rate was associated with clinical remission of depressive symptoms (Traskman-Bendz et al., 1984; van Praag, 1977). Pointing in the same direction are the pleasant psychopathological effects of "ecstasy" (methylenedioxymetamphetamine, MDMA), which is most likely to act by inducing serotonin release (Huether et al., 1997). These observations indicate that an increase in synaptic serotonin concentrations may not represent the neurobiological correlate of punishment but rather induce a reduction in anxiety and depression.

Some studies indicate that the association between a low serotonin turnover rate and aggressive behavior may be mediated by negative emotions, such as feeling insecure and threatened. Virkunnen et al. (1994) observed that alcoholics with low serotonin turnover and high aggressiveness suffer from increased anxiety (Virkunnen et al., 1994). In a study by Knutson et al. (1998), the primary correlate of SSRI-induced increases in synaptic serotonin was decreased anxiety and insecurity, whereas the reduction in aggressiveness was statistically explained by the decrease in negative emotions (Knutson et al., 1998). The reduction in aggressiveness may thus be due to a decrease in perceptions of insecurity or threat. This interpretation is supported by animal experiments showing that increased serotonin turnover is associated with social competence in competitive games (Knutson et al., 1996a), whereas serotonin depletion induced insecure and anxious behavior patterns (Knutson et al., 1996b).

Serotonergic Dysfunction and Negative Mood States

A brain imaging study of abstinent alcoholics supported the hypothesis that serotonergic dysfunction may be associated with negative mood states, such as depression and anxiety. Among male alcoholics who had abstained from alcohol for more than four weeks, serotonin transporters in the raphe area of the brainstem were significantly reduced compared with healthy control subjects (Heinz et al., 1998b). The reduction in raphe serotonin transporters correlated with the amount of lifetime alcohol intake, indicating that the reduced serotonin transporter availability may be the consequence of chronic alcohol intoxication. Clinically, the reduction in serotonin transporters was correlated with the severity of negative mood states but not with impulsivity (Heinz et al., 1998b). Interestingly, a reduction in availability of raphe serotonin transporters has also been observed in patients with major depression (Malison et al., 1998).

These observations on the role of serotonin in anxiety and depression support the hypothesis of Hellhammer (1993), who claimed that the serotonergic system is involved in "trophotropic (regenerative) behavior patterns" and "supports regenerative behavior such as food consumption and digestion, relaxation, growth, sleep, passivity and inactivity" (Hellhammer, 1993). A similar interpretation was advanced by McCormick (1992) and Baumgarten and Grozdanovic (1995), who suggested that serotonergic neurotransmission supports a "protective filter effect" by modulating thalamocortical circuits, reducing the impact of sensory inputs. Increased serotonergic neurotransmission may thus promote a feeling of security and tranquility (Knutson et al., 1996a; Raleigh et al., 1988), whereas subjects with a deficit in serotonergic neurotransmission may feel insecure and threatened (Clarke et al., 1996; Higley et al., 1991; Jones et al., 1992). In this view, the manifestation of aggressiveness or clinical depression after serotonin de-

pletion is a secondary consequence from general feelings of tension and insecurity (Knutson et al., 1998) and may depend on the manifestation of other causal factors, such as learned behavior in social contexts (Kraemer and McKinney, 1979; Raleigh and McGuire, 1991). If type 2 alcoholism is best understood as a comorbidity of alcoholism and antisocial personality disorder (Irwin et al., 1990; Schuckit et al., 1995), the interaction of insecurity, anxiety, and alcohol-associated behavior disinhibition may result in violent behavior.

It is important to note that the observed reduction in serotonin transporters of abstinent alcoholics was not limited to patients with an early onset of alcoholism (Heinz et al., 1998b). These observations extend the relevance of serotonergic dysfunction to a larger group of alcoholics, who may not suffer from a primary deficit in the serotonin turnover rate but who experience negative mood states in association with toxic effects of chronic alcohol intake on serotonergic neurotransmission. Because negative mood states interact with the long-term risk of relapse in abstinent alcoholics (Hartka et al., 1991; Wagner Glenn and Parsons, 1991), a loss of serotonin transporters may contribute to the maintenance of alcohol dependence. The association between clinical depression and the risk of relapse is not linear, however: in follow-up studies, negative mood states below the level of major depression were associated with an increased risk of relapse only when subjects were followed up for more than two years (Hartka et al., 1991). Within the first months of abstinence, negative mood states were instead associated with a *reduced* risk of relapse (Hartka et al., 1991; Heinz et al., 1996). The explanation for this surprising finding may be the strong association between anxiety, depression, and harm avoidance, which may render subjects more cautious and risk-adverse during early abstinence (Hartka et al., 1991). This observation may help to explain why administration of SSRIs does not strongly affect the risk of relapse among alcoholics (Heinz, 1999b). In the absence of major depression, increased anxiety and harm avoidance seem to reduce the risk of relapse in the first month of abstinence (Heinz et al., 1996); therefore, the treatment of negative effects with SSRIs may not favorably affect treatment outcome unless the observation period is prolonged.

Genotype Effects on Raphe Serotonin Transporters

The reduction in raphe serotonin transporter among abstinent alcoholics may occur primarily in a genetically defined subgroup of alcoholics (Heinz et al., 2000). A functional variant was described in the promoter region of the gene, *SLC6A4* (Lesch et al., 1996). The two abundant alleles at this polymorphism within the serotonin transporter (5-HTT) promoter are designated long (*l*) or short (*s*) on the basis of the number of copies of an imperfect repeat sequence they contain. Homozygosity for the long allele of the 5-HTT promoter (*ll* homozygosity) had in vitro been associated with an increased density and functional capacity of the human serotonin transporter (Lesch et al., 1996). In two studies, *ll* homozygotic subjects displayed lower levels of anxiety and depression, although the effect size was rather small (Lesch et al., 1996; Mazzanti et al., 1998) and other studies did not replicate the finding (Edenberg et al., 1998; Gelernter et al., 1997). A brain imaging study with β-CIT and SPECT observed an in vivo relationship of 5-HTT promoter genotype to serotonin transporter availability in the dorsal brainstem raphe area of male volunteers (Heinz et al., 2000). From their in vitro work, Lesch et al. had predicted that subjects carrying the *ll* genotype should have a 1.9- to 2.2-fold increase in the functional capacity of serotonin transporters (Lesch et al., 1996). In fact, the in vivo increase in raphe serotonin transporters of *ll*-homozygotic male volunteers was well within this range (Heinz et al., 2000). The study is limited by small sample size; however, an autoradiographic study by Little and coworkers (1998) also showed that in healthy control subjects, serotonin transporter density is increased among *ll* homozygotes compared with *s* carriers. These results indicate that *ll* homozygotic subjects in vitro and in vivo have an increased availability of serotonin transporters.

Among male alcoholics who had chronically consumed alcohol, the 5-HTT genotype may also render subjects specifically vulnerable. Alcohol-dependent patients and male control subjects who carried the short allele of the 5-HTT promoter did not differ in their serotonin transporter availability; however, a significant reduction in raphe serotonin transporters was found among alcoholics with the *ll* genotype exclusively. The reduction was correlated with the level of chronic alcohol intake and may be the result rather than the cause of excessive alcohol consumption (Heinz et al., 2000). If so, carrying the *ll* genotype may render subjects more vulnerable to the long-term, toxic effects of chronic alcohol intake. In the autoradiographic study (Little et al., 1998), alcoholics with the *ll* genotype also showed a lower serotonin transporter density compared with *s* carriers. In this in vitro study, however, serotonin transporter density seemed to be higher in both genotypes than in the in vivo data (Heinz et al., 2000), which may be due to in vivo competition between the radioligand β-CIT and endogenous serotonin. In fact, in vivo restoration of the synaptic serotonin content after serotonin depletion was associated with a significant decrease in β-CIT binding to raphe serotonin transporters (Jones et al., 1998). This observation supports the hypothesis that endogenous serotonin competes with the radioligand β-CIT for binding at serotonin transporters, so that the in vivo transporter availability may be lower than the transporter density assessed in vitro.

SEROTONERGIC DYSFUNCTION AND RESPONSE TO ALCOHOL INTAKE

One of the dispositional factors toward excessive alcohol intake and alcoholism seems to be a low response to the

acute effects of alcohol intake (Schuckit and Smith, 1996). In a behavioral sense, alcohol intake may be more rewarding if there are only a few negative effects of alcohol intake, such as ataxia or sedation, and a low response to alcohol intoxication may be especially important among young men who misinterpret the ability to consume a large quantity of alcohol as a sign of male competence. A low-level response to alcohol seems to be partly inherited, because it is found in young men with a positive family history of alcoholism (Newlin and Thompson, 1990; Pollock, 1992; Schuckit and Smith, 1996) and is influenced by genetic factors in twin studies (Madden et al., 1995; Rose et al., 1994). In rats, diminished acute sensitivity to alcohol is a selectable trait (McBride and Li, 1998). A clue to the genetic basis of alcohol sensitivity was recently found by observing an association with a functional 5-HTT variant (Türker et al., 1998). The subjects assessed in this study, however, were not separated into social drinkers, alcohol abusers, or alcoholics. Moreover, the low alcohol response was not associated with one of the genotypes (*ll* homozygosity versus *s* carriers) that differ in their in vitro and in vivo expression of serotonin transporters (Heinz et al., 2000; Lesch et al., 1996; Little et al., 1998). Such an association was observed in a prospective study (Schuckit et al., 1999) that assessed young men for their alcohol sensitivity and then followed them up for diagnostic outcome over 15 years. In these men, an initially low response to alcohol was associated with the *ll* genotype (Schuckit et al., 1999), indicating that these men had increased availability of serotonin transporters when they first experienced low effects of alcohol consumption (Heinz et al., 2000; Lesch et al., 1996; Little et al., 1998). Schuckit and coworkers (1999) suggested that an increased availability of serotonin uptake sites may be associated with reduced serotonin concentrations in the synapse. Such a negative correlation was found in nonhuman primates, who displayed a low serotonin turnover rate and a high availability of raphe serotonin transporters in association with a high alcohol tolerance (Heinz et al., 1998a). These observations indicate that an increased availability of serotonin transporters and a low serotonin turnover rate may be associated with a low response to alcohol, one of the important predisposing factors to excessive alcohol intake and alcoholism (Schuckit and Smith, 1996; Schuckit et al., 1999).

Several studies indicate that the genetic composition of the serotonin transporter may not by itself predispose to alcohol dependence. Sander and coworkers (1998) published a finding in 1998 that the short allele of the serotonin transporter was associated trendwise with alcoholism and reported an even weaker association with antisocial personality disorder among the alcoholics. The studies by Gelernter et al. (1997) and Edenberg et al. (1998), however, found no association between serotonin transporter genotype and alcohol dependence. Likewise, no association between alcoholism and 5-HTT genotype was found in a much smaller sample (Heinz et al., 2000). These findings indicate that the genetic composition of the serotonin transporter may be associated with a tendency toward alcoholism only in combination with other genotypes affecting the brain's excitatory and sedative balance. Among primates that underwent early social stress, a low response to alcohol was correlated with a low serotonin turnover rate and an increased availability of serotonin transporters, independent of the 5-HTT genotype (Heinz et al., 1998a). Environmental factors may thus induce phenocopies of serotonergic dysfunction that reduce the statistical association of 5-HTT promoter genotype and alcohol tolerance.

In the study by Schuckit and coworkers (1999), an allelic variance of the $GABA_{A\alpha6}$ receptor, the so-called Pro/Ser genotype, was also associated with a low acute alcohol response. All subjects with both the *ll* genotype of the 5-HTT promoter and the Pro/Ser genotype of the $GABA_{A\alpha6}$ receptor later developed alcohol dependence. This observation may indicate that the serotonin transporter genotype increases the risk of alcohol-related problems only in interaction with other neurotransmitter systems, such as GABA-ergic neurotransmission. This hypothesis is supported by the observation that nonhuman primates with a low serotonin turnover rate showed decreased effects of GABA-ergic sedation on orbitofrontal glucose utilization (Doudet et al., 1995). Delayed or reduced alcohol-induced sedation in subjects with a low serotonin turnover rate may increase the psychomotor stimulant and rewarding effects of ethanol-induced dopamine release in the ventral striatum. Alcohol intake interacts with striatal dopamine release via $5\text{-}HT_2$ and $5\text{-}HT_3$ receptors (Carboni et al., 1989; Heinz et al., 1998c; Wallis et al., 1993). Low doses of alcohol intake induce a dopamine-mediated psychomotor stimulation, whereas high-dose alcohol consumption results in potentially GABA-ergic sedation (Di Chiara and Imperato, 1988; Gessa et al., 1985; Imperato and Di Chiara, 1986). It is possible that strong psychomotor stimulation and delayed sedation after alcohol intake are factors predisposing to excessive alcohol intake. GABA-ergic glutamatergic, and opioidergic neurotransmitter systems probably interact with the serotonergic and dopaminergic systems in the feedback circuitry and pathogenesis of alcohol dependence (Diana et al., 1993; Di Chiara et al., 1996; Tao and Auerbach, 1995). These observations indicate that the observed association between serotonin transporter function and the effects of alcohol intake may be mediated by an interaction with GABA-ergic neurotransmission. Further studies will have to assess whether a reduction in GABA-ergic sedation is also involved in the pathogenesis of negative affects, mediated hypothetically by a lack of "protective filter effect," and feelings of insecurity and anxiety (Baumgarten and Grozdanovic, 1995; Knutson et al., 1998; McCormick, 1992).

CONCLUSION

A series of studies observed an association between serotonergic dysfunction and negative mood states (Knutson et al., 1998; Meltzer et al., 1994; van Praag, 1977). If a low

serotonin turnover rate is present early during individual development (Higley et al., 1991), impulsive aggressiveness may develop and contribute to some behavioral traits of early-onset alcoholics (Fils-Aime et al., 1996; Heinz et al., 1998a). After chronic alcohol intake, serotonergic dysfunction was associated with depression and anxiety (Heinz et al., 1998b), which interact with the long-term risk of relapse (Hartka et al., 1991). In some recent studies, serotonergic dysfunction was also associated with a low alcohol response (Doudet et al., 1995; Heinz et al., 1998a; Schuckit et al., 1999). Among nonhuman primates, serotonergic dysfunction was correlated with a low response to both alcohol and aggressiveness (Heinz et al., 1998a). A low response to ethanol and increased aggressiveness was also found in mice lacking the 5-HT_{1B} receptor (Coccarro et al., 1989; Saudou et al., 1994). Further studies are necessary to examine the relationship between these two behavioral phenotypes and the pathogenesis and maintenance of alcoholism.

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